

Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 30073P WO	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/EP2004/002850	International filing date (day/month/year) 18.03.2004	Priority date (day/month/year) 19.03.2003
International Patent Classification (IPC) or national classification and IPC		
<p>Applicant KTB TUMORFORSCHUNGS GMBH</p>		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of **8** sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
 - a. (*sent to the applicant and to the International Bureau*) a total of _____ sheets, as follows:
 - sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
 - sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
 - b. (*sent to the International Bureau only*) a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

<input checked="" type="checkbox"/>	Box No. I	Basis of the report
<input type="checkbox"/>	Box No. II	Priority
<input checked="" type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
<input type="checkbox"/>	Box No. IV	Lack of unity of invention
<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
<input type="checkbox"/>	Box No. VI	Certain documents cited
<input type="checkbox"/>	Box No. VII	Certain defects in the international application
<input type="checkbox"/>	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/EP	Authorized officer
Facsimile No.	Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/EP2004/002850

Box No. I

Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

- This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:
- international search (Rule 12.3 and 23.1(b))
 - publication of the international application (Rule 12.4)
 - international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

- the international application as originally filed/furnished
 the description:

pages 1-18 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

- the claims:

nos. 1-15 as originally filed/furnished

nos.* 19-24 as amended (together with any statement) under Article 19

nos.* _____ received by this Authority on _____

nos.* _____ received by this Authority on _____

- the drawings:

sheets 1/1 as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

- a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. The amendments have resulted in the cancellation of:

- the description, pages _____
- the claims, nos. _____
- the drawings, sheets/figs _____
- the sequence listing (*specify*): _____
- any table(s) related to sequence listing (*specify*): _____

4. This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- the description, pages _____
- the claims, nos. _____
- the drawings, sheets/figs _____
- the sequence listing (*specify*): _____
- any table(s) related to sequence listing (*specify*): _____

* If item 4 applies, some or all of those sheets may be marked "superseded."

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Box No. III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

the entire international application

claims Nos. 14

because:

the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international preliminary examination (*specify*):

Claim 14 relates to subject matter which, in the opinion of this Authority, falls under PCT Rule 67.1(iv). Consequently, no expert opinion has been established in respect of the industrial applicability of the subject matter of said claims (PCT Article 34(4)(a)(i)).

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

no international search report has been established for said claims Nos. _____

the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

has not been furnished

does not comply with the standard

the computer readable form

has not been furnished

does not comply with the standard

the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	<u>1-15</u>	YES
	Claims	_____	NO
Inventive step (IS)	Claims	<u>1-15</u>	YES
	Claims	_____	NO
Industrial applicability (IA)	Claims	<u>1-13, 15</u>	YES
	Claims	_____	NO

2. Citations and explanations (Rule 70.7)

Reference is made to the following documents:

- D1: PASHKOVSKII F.S., KHBEBNIKOVA T.S.,
 LAKHVICH F.A.: "GENERAL APPROACH TO SYNTHESIS
 OF CARBOPLATIN ANALOGUE CONTAINING FRAGMENTS
 OF CARBOXYLIC FATTY ACIDS IN ACID LIGAND",
 BELARUSKAYA NAVUKA, vol. 46, no. 4, 2002,
 pages 63-65, XP009033021
- D2: US-A-5 011 959 (KHOKHAR ABDUL R)
 30 April 1991 (1991-04-30)
- D3: BOECKLER C ET AL: "Immunogenicity of new
 heterobifunctional cross-linking reagents
 used in the conjugation of synthetic peptides
 to liposomes", JOURNAL OF IMMUNOLOGICAL
 METHODS, ELSEVIER SCIENCE PUBLISHERS B.V.,
 AMSTERDAM, NL, vol. 191, no. 1, 10 May 1996
 (1996-05-10), pages 1-10
 XP004020848 ISSN: 0022-1759
- D4: LEBWOHL D ET AL: "Clinical development of
 platinum complexes in cancer therapy: an
 historical perspective and an update", EUROPEAN
 JOURNAL OF CANCER, PERGAMON PRESS, OXFORD, GB,
 vol. 34, no. 10, September 1998 (1998-09),
 pages 1522-1534, XP004285042 ISSN: 0959-8049.

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

The application relates to low molecular weight platinum complexes of cyclobutan-1,1-dicarboxylate ligands, which contain a protein-binding group, and to the production and use thereof.

1. PCT Article 33(2)

The aforementioned documents D1, D2 and D4, cited in the search report, relate to carboplatin analogues. However, only D1 discloses a linker bound to the cyclobutane substructure.

Although document D1 discloses carboplatin analogues containing fragments of saturated or unsaturated carboxylic acids in the acidic ligand, *inter alia* the cis-diammine[3-(octadeca-9,12-dieneamido)-1,1,-cyclobutanedicarboxylato]platinum (II), the subject matter of the present application can be considered novel (PCT Article 33(2)) in view of the absence of the protein-binding group in these complexes.

2. PCT Article 33(3)

The technical problem addressed by the application can be considered to be that of identifying further carboplatin derivatives that can be used for treating cancer (see figure 1).

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Box No. V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The solution to the above problem, as proposed in the present application, lies in devising carboplatin derivatives that contain a protein-binding group. As a result, the claimed platinum complexes bind rapidly and covalently to serum proteins via the protein-binding group, a macromolecular transport form of the active ingredient being thereby generated.

The closest prior art is document D1, which also discloses carboplatin analogues, the linker thereof being likewise bound to the cyclobutyl ring. However, this linker is a fatty acid linker that contains neither repetitive ethoxy groups nor a protein-binding group. In consequence, the carboplatin analogues of D1 do not have covalent protein-binding properties.

Polyoxyethylene linkers with a thiol-binding group, which is suitable *per se* for binding to free cystein groups on the surface of proteins, were disclosed in document D3 (published in 1996). However, since these are used for liposomal systems and D3 contains nothing to suggest that they can be attached to platinum compounds, said document cannot be used as evidence against the involvement of an inventive step in the present application.

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Box No. V**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

For this reason, the present application is considered to involve an inventive step (PCT Article 33(3)).

3. (PCT Article 34(4))

The PCT Contracting States do not have uniform criteria for assessing the industrial applicability of the subjects of claim 14 in its present form. Patentability may also depend on the wording of the claims. The EPO, for example, does not recognise the industrial applicability of claims to the medical use of a compound; it may, however, allow claims to the first medical application of a known compound or to the use of such a compound in the manufacture of a drug for a new medical application.